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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TSAY, MARSHA M	
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1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,878	VAN ES ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 24, 2008 has been entered.

Claim 8 is canceled. Claims 1-7, 9-30 are currently under examination.

Priority: The request for priority to EPO 03077451.7, filed August 5, 2003, is acknowledged.

Objections and Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "essentially similar" in claims 24 and 30 are relative terms which render the claims indefinite. The terms "essentially similar" are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 24 and 30 recite region. It is unclear what is meant by "region", i.e. which region, how big is the region, etc. Further clarification is requested.

Claims 25-29 are included in this rejection because they are dependent on claim 24.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (WO 0134801; IDS, previously cited) in view of Wang (Wang 2000 International Journal of Pharmaceutics 203: 1-60) as evidenced by Matveev et al. (1997 Food Hydrocolloids 11(2): 125-133; previously cited). Matveev et al. has been used as evidence that gelatin has a glass transition temperature of 200° C (p. 129).

For the purpose of prior art, claim 24 is interpreted to mean the complete amino acid sequence of the recombinant or synthetic gelatin-like polypeptide can be similar to a complete amino acid sequence of a native collagen since it is unclear which region of the native collagen, said claim is referring to.

Chang et al. disclose vaccines comprising recombinant gelatin and a method of producing such vaccines. Chang et al. disclose a dried vaccine formulation comprising recombinant gelatin (p. 85 line 9, p. 86 line 29; claim 1) or lyophilized vaccines comprising using recombinant gelatin as a stabilizer (p. 61 lines 35-38; claim 1). Accordingly, the recombinant gelatin is essentially a polymer that stabilizes the pharmaceutical formulation and should have characteristics similar to an animal-source gelatin, i.e. MW, melting temperatures, etc. (p. 65 lines 21-33). Therefore, the use of recombinant gelatin offers the advantage of reducing the risk

of unwanted immune responses from the gelatin itself (col. 59 lines 12-19). Chang et al. disclose the recombinant gelatin can be derived from a human sequence or animal sources (p. 59 lines 16-19), wherein the term "derivative" encompasses those molecules containing at least one structural and/or functional characteristic of the molecule from which it is derived (p. 15 lines 11-15). It is known that gelatin comprises consecutive Gly-Xaa-Yaa triplets. The recombinant gelatin can have a molecular weight range between 0 kDa to 350 kDa (p. 85 lines 22-26; claims 2-3). Chang et al. also disclose a method of producing a composition comprising a vaccine and recombinant gelatin (p. 88 lines 25-32; claim 9). In a non-limiting example, i.e. Example 4, Chang et al. disclose the expression of a non-hydroxylated recombinant human gelatin, which would inherently be free of a helical structure (p. 73 lines 5-10; claims 1, 6-8, 15-20). Further, Chang et al. disclose the recombinant gelatins can possess particular ranges of molecular weights (p. 63 lines 30-32, example 1; claims 5, 12-14). Chang et al. do not teach a glass transition temperature for gelatin.

Wang et al. disclose that lyophilized proteins need stabilization in the solid state to survive long-term storage as pharmaceuticals (p. 25 col. 2). Accordingly, the glass transition temperature of protein formulations is considered to be one of the major determinants of protein stability (p. 28 col. 2). Wang et al. disclose that generally the higher the glass transition temperature of the polymer in said formulation, the more stable the protein formulation; therefore, the glass transition temperature may be used as a guiding parameter to screen protein stabilizers, i.e. by DSC (p. 28 col. 2 to p. 29 col. 1). In Tables 1 (p. 19) and 2 (p. 39), Wang et al. disclose gelatin can be used as a polymer to stabilize lyophilized pharmaceuticals.

It is known in the art that gelatin has a calculated glass transition temperature of 200° C (p. 129) and an experimental glass transition temperature determined by DSC of 217° C (p. 132).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Chang et al. by producing a lyophilized composition comprising a protein drug and a recombinant gelatin such that said recombinant gelatin has a polypeptide sequence that is a native mammalian collagen sequence having a high glass transition temperature (as suggested by Wang), where said recombinant gelatin has the same functional and/or structural characteristics as said native collagen, i.e. having a glass transition temperature of 200° C (as evidenced by Matveev et al.) (claims 1-7, 9-30). Since Chang et al. disclose that recombinant gelatin comprising a native collagen sequence can minimize immune response and can be used as a stabilizer in lyophilized vaccine formulations and Wang further discloses that polymers having a high glass transition temperature provide the most stability to a protein formulation, one of ordinary skill would be motivated to produce a recombinant gelatin that has a high glass transition temperature at least equivalent to native collagen (i.e. 200° C) since Wang discloses that generally the higher the glass transition temperature of a polymer, the more stability it imparts on a lyophilized pharmaceutical composition.

The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). In this instance, the motivation would be to produce a recombinant gelatin sequence having a mammalian gelatin sequence that also has a glass transition temperature at least equivalent to native gelatin.

The previous 103(a) rejection of Chang et al. in view of Matveev et al. has been withdrawn. However, the instant claims are still believed to be unpatentable over Chang et al. in view of Wang. The Matveev et al. reference has been used for evidence.

In their remarks, Applicants assert (1) independent claims 1 and 9 provide the benefit of an improved stability of the claimed composition. This result is not predictable from either Chang et al. or Matveev et al., neither of which document indicates that the stability of a lyophilized composition comprising a physiologically active agent can be improved by employing a recombinant or synthetic polypeptide in the composition. (2) Applicants believe that a person of ordinary skill following Chang et al.'s suggestion to employ a recombinant gelatin having similar properties to gelatin isolated from animals and looking at the glass transition temperatures mentioned in Matveev et al. would not be able to provide the claimed composition and method because Chang et al. do not appear to disclose a method of preparing a recombinant or synthetic gelatin-like polypeptide meeting the requirements of Applicants' claims 1 and 9 with regard to a calculated glass transition temperature of higher than 180° C. (3) Neither Chang et al. nor Matveev et al. appear to disclose or suggest that a native polypeptide sequence can include a region that has a calculated glass transition temperature which is higher than that of the complete sequence of the native polypeptide, and that this region can be identified and utilized to improve the stability of vaccines and other physiologically active products. (4) While Chang et al. disclose that polypeptides having various molecular weights, degrees of hydroxylation and/or cross-linking can be employed in vaccine compositions, Chang et al. do not appear to disclose that a higher polypeptide glass transition temperature can improve

vaccine stability. (5) It is unclear what Chang et al. mean by the recombinant gelatin is "derived" from animal sources. Applicant's arguments have been fully considered but they are not persuasive.

(1a) Chang et al. disclose recombinant gelatin offers an advantage in that gelatin derived from human collagen sequence reduces the risk of immunogenicity and/or antigenicity from the gelatin in itself (p. 59 lines 12-14). Chang et al. further disclose that the gelatin serves as a stabilizer in the pharmaceutical formulation (p. 65 lines 21-30). Therefore, Chang et al. does indicate that recombinant gelatin functions to improve the stability of a pharmaceutical active agent. Further, the newly cited Wang reference discloses that gelatin improves the stability of a lyophilized composition comprising a physiologically active agent.

(2a) The Matveev et al. has been withdrawn as a reference but is still used as evidence that native gelatin has a calculated glass transition temperature of 200° C. Chang et al. disclose that the recombinant gelatin can comprise a native mammalian gelatin sequence (p. 59 lines 12-19). Chang et al. further disclose that said gelatin is used as a stabilizer in the lyophilized vaccine formulation (p. 65 lines 21). The newly cited Wang reference discloses that generally the higher the glass transition temperature, the more stable the lyophilized protein is (p. 28). Wang further discloses that DSC can be used as a guiding parameter to screen protein stabilizers (p. 28-29); which is used in Example 2 of the instant specification as a means of measuring the glass transition temperature. Since it is known in the art that native gelatin has a calculated glass transition temperature of 200° C (as evidenced by Matveev et al.), it would be reasonable for one of ordinary skill in the art to recognize that the recombinant gelatin used in a lyophilized

pharmaceutical formulation should ideally have a glass transition temperature of at least 200° C since native gelatin has a calculated value of 200° C and Chang et al. disclose that said recombinant gelatin should have the same functional and structural characteristics as native gelatin and Wang discloses that polymers having a high glass transition temperature improves the stability of a lyophilized pharmaceutical active agent.

(3a) Independent claims 1 and 9 do not recite a specific region within a native gelatin/collagen sequence; therefore, it would appear that the instant lyophilized composition can comprise a recombinant gelatin that comprises a full-length native collagen sequence. Further, while claims 24 and 30 recite a region of the amino acid sequence of a native collagen, it is unclear what constitutes a "region"; therefore a "region" can still encompass the full-length native collagen sequence minus 1-2 amino acid residues.

(4a) The deficiency of Chang et al. to disclose that a higher polypeptide glass transition temperature can improve vaccine stability is believed to be remedied by the newly cited Wang reference.

(5a) The term "derivative" as used in Chang et al. encompasses those molecules containing at least one structural and/or functional characteristic of the molecule form which it is derived (p. 15). Since the recombinant gelatins would contain at least one structural characteristic of native collagen and is "derived" from a mammalian sequence and produced recombinantly (p. 59 lines 10-28), it would be reasonable for one of ordinary skill to recognize that the recombinant gelatins of Chang et al. can be recombinantly produced to comprise the amino acid sequence of a native collagen.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

December 17, 2008